

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

DANILO PORRO
MICHAEL SAUER

Serial No.: 10/606,300

Filed: June 25, 2003

For: ASCORBIC ACID PRODUCTION FROM
YEAST

Confirmation No.: 8974

Group Art Unit: 1636

Examiner: Walter Schlapkohl

Attorney Docket: 2027.594097/RFE
(2005942)

CUSTOMER NO. 23720

APPEAL BRIEF

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

Sir:

Applicants hereby submit this Appeal Brief to the Board of Patent Appeals and Interferences in response to the final Office Action dated October 6, 2006. The fee for filing this Appeal Brief is \$500.

The Director is authorized to deduct the fee relating to the enclosed material under 37 C.F.R. §§ 1.16 to 1.21 from Williams, Morgan & Amerson, P.C. Deposit Account No. 50-0786/2027.594097RE.

I. REAL PARTY IN INTEREST

The assignee of the present patent application is Università Degli Studi di Milano, Bicocca, having a place of business at Piazza dell'Ateneo Nuovo I, Milano (Milan), Italy 20126.

II. RELATED APPEALS AND INTERFERENCES

None.

III. STATUS OF THE CLAIMS

Claims 12-14 have been rejected and are the subject of this appeal.

IV. STATUS OF AMENDMENTS

Applicant did not file any amendments after mailing of the final rejection.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Claim 12 is directed to a method of generating ascorbic acid (p. 6, lines 26-29; p. 11, lines 22-25). The method comprises obtaining a recombinant yeast capable of converting an ascorbic acid precursor into ascorbic acid (p. 11, line 26 to p. 12, line 29), wherein the yeast is functionally transformed with a coding region encoding L-galactose dehydrogenase (LGDH) enzyme (p. 12, line 30 to p. 13, line 1) having at least about 90% similarity with SEQ ID NO:11 (p. 13, lines 14-16 and 24-25). The method comprises culturing the recombinant yeast in a medium comprising an ascorbic acid precursor, thereby forming ascorbic acid (p. 9, line 28 to p. 10, line 29; p. 17, lines 3-4 and 29-31). The method comprises isolating the ascorbic acid (p. 11, lines 1-19; p. 18, line 12). The skilled artisan will understand “at least about 90% similarity” in this context to refer to amino acid sequences which, when aligned with SEQ ID NO:11, have the same or a similar amino acid as SEQ ID NO:11 at at least about 90% of amino acid residues.

The skilled artisan will understand “similar” as referring to amino acids having comparable structures, polarities, and electrical charges at neutral (7.0) or physiological (7.4) pH. Examples of similar amino acids include, but are not limited to, leucine and isoleucine; serine and threonine; arginine and lysine; and aspartate and glutamate.

Claim 13 is directed to a method of generating ascorbic acid. The method comprises obtaining a recombinant yeast capable of converting an ascorbic acid precursor into ascorbic acid, wherein the yeast is functionally transformed with a coding region encoding L-galactose dehydrogenase (LGDH) enzyme having at least about 90% identity with SEQ ID NO:11 (p. 13, lines 26-28; p. 14, lines 5-6). The method comprises culturing the recombinant yeast in a medium comprising an ascorbic acid precursor, thereby forming ascorbic acid. The method comprises isolating the ascorbic acid. The skilled artisan will understand “at least about 90% identity” in this context to refer to amino acid sequences which, when aligned with SEQ ID NO:11, have the same amino acid as SEQ ID NO:11 at at least about 90% of amino acid residues.

Claim 14 is directed to a method of generating ascorbic acid. The method comprises obtaining a recombinant yeast capable of converting an ascorbic acid precursor into ascorbic acid, wherein the yeast is functionally transformed with a coding region encoding L-galactose dehydrogenase (LGDH) enzyme and the coding region encoding the LGDH enzyme has at least about 90% identity with SEQ ID NO:12 (p. 14, lines 7-9 and 17-18). The method comprises culturing the recombinant yeast in a medium comprising an ascorbic acid precursor, thereby forming ascorbic acid. The method comprises isolating the ascorbic acid. The skilled artisan will understand “at least about 90% identity” in this context to refer to nucleotide sequences

which, when aligned with SEQ ID NO:12, have the same nucleotide as SEQ ID NO:12 at at least about 90% of nucleotide positions.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Do claims 12-14 fail to comply with the written description requirement of 35 U.S.C. §112, first paragraph?

In the final Office Action dated October 6, 2006, the Examiner also imposed a nonstatutory obviousness-type double patenting rejection of claims 12-14 over claims 1-9 of U.S. Pat. No. 6,630,330. Applicants filed a terminal disclaimer over the '330 patent on October 20, 2006, and therefore submit there is no need to review the double patenting rejection on appeal.

VII. ARGUMENT

A. Patentability of claims 12-14 under 35 U.S.C. §112, first paragraph

The written description requirement set forth in 35 U.S.C. §112, first paragraph implements the principle that a patent must describe the technology that is sought to be patented. The written description requirement also conveys that an applicant has invented the subject matter which he claims.

In the Office Action dated October 6, 2006, the Examiner alleged claims 12-14 lacked sufficient written description “because one of ordinary skill in the art would not know which embodiments encompassed within the genus of enzymes with 90% identity or with 90% similarity to SEQ ID NO:11 or encoded by a coding region having 90% identity to SEQ ID NO:12 would be functional in a method of making ascorbic acid” (Detailed Action, p. 4). He further alleged that the structural and functional characteristics recited by claims 12-14, specifically, a coding region encoding L-galactose dehydrogenase (LGDH) enzyme meeting the recited criteria, “merely provide an invitation to conduct experiments to determine which

sequences within the claimed genus would meet the functional criteria recited in the claims” (Detailed Action, p. 5). He further argued “Which variants of SEQ ID NO:11 and 12, if any, does Applicant possess that are NOT deleterious variants with regard to LGDH function?” which implies the Examiner read the written description requirement as *per se* requiring Applicants to present multiple sequences usable in the claimed method. He also alleged “one of ordinary skill in the art would not know which variants are or are NOT deleterious.”

In *Capon v. Eshhar*, 76 USPQ2d 1078 (Fed. Cir. 2005), the United States Court of Appeals for the Federal Circuit addressed the written description requirement and also touched on its relationship to the enablement requirement and issues of claim scope. The present specification, in light of the holdings in *Capon v. Eshhar*, supports Applicants’ contention that claim 12 complies with the written description requirement.

The specification defines L-galactose dehydrogenase (LGDH) at p. 19, lines 16-18, as “a protein that catalyzes the conversion of L-galactono-1,4-lactone + 2 ferricytochrome c to L-ascorbic acid + 2 ferrocytochrome c.” To paraphrase, any protein that catalyzes the stated reaction is an L-galactose dehydrogenase, or LGDH. This statement is supported by the reference at p. 19, line 16, of LGDH as “Enzyme 1.3.2.3.” The skilled artisan will understand this is a reference to the Enzyme Commission (EC) and will also understand that an EC number technically refers, *not* to a specific protein, but to a specific reaction catalyzed by *any* protein. It is clear that “L-galactose dehydrogenase” or “LGDH,” as used in the present specification, was a term having a plain and precise meaning well-known in the art as of the priority date of the present application.

As will be clear, L-galactose dehydrogenase encompasses a large number of proteins that catalyze the conversion of L-galactono-1,4-lactone + 2 ferricytochrome c to L-ascorbic acid + 2

ferrocytochrome c. The present claims are narrower in scope, reciting not LGDH *per se* but to LGDHs having at least about 90% similarity with SEQ ID NO:11 (claim 12), having at least about 90% identity with SEQ ID NO:11 (claim 13), or being encoded by a coding region having at least about 90% identity with SEQ ID NO:12 (claim 14).

On their face, the teachings of the specification relating to the recited LGDHs comply with the purposes of the written description requirement; the public receives meaningful disclosure of what Applicants invented, as the genera of recited LGDHs have clear metes and bounds and clear instruction for practicing the invention upon its future entry into the public domain, and also to clearly convey that Applicants invented what they claim.

It is true that Applicants only enumerated LGDHs having SEQ ID NO:11 or encoded by SEQ ID NO:12. Even so, LGDHs having at least about 90% similarity or at least about 90% identity with SEQ ID NO:11 or being encoded by a coding region having at least about 90% identity with SEQ ID NO:12 possess sufficient written description, for several reasons. First, as will be apparent to the skilled artisan, there are a vast number of, for example, LGDHs having at least about 90% identity to SEQ ID NO:11. SEQ ID NO:11 is a polypeptide having 321 amino acids. If we hypothetically only consider other sequences having 291 amino acids in common (differing in 30, and therefore having at least about 90% identity), there are $321! / (291! * 30!)$, more than 3.4×10^{41} , such other sequences. If we hypothetically only consider other sequences having 311 amino acids in common (differing in 10, and therefore having about 97% identity), there are $321! / (311! * 10!)$, more than 2.4×10^{18} , such other sequences. The impossibility of listing every such sequence is apparent. However, listing every such sequence is not required; as the Court held in *Capon v. Eshhar*, there is no *per se* rule that a sequence listing must be presented for every biological sequence claimed in a patent application. 76 USPQ2d at 1084-

1085. This is in contrast to the Examiner's implication referred to above. Also as held in *Capon v. Eshhar*, the written description requirement "does not state that every invention must be described in the same way. As each field evolves, the balance also evolves between what is known and what is added by each inventive contribution." *Id.*, at 1085.

Many of the Examiner's arguments in the final Office Action are related to claim scope, e.g., the skilled artisan would allegedly not know which embodiments encompassed within the genus of enzymes with 90% identity or with 90% similarity to SEQ ID NO:11 or encoded by a coding region having 90% identity to SEQ ID NO:12 would be functional in a method of making ascorbic acid, that the claims merely provide an invitation to conduct experiments to determine which sequences within the claimed genus would meet the functional criteria recited, and that one of ordinary skill in the art would not know which variants are or are not deleterious; the Examiner alleged that the inclusion of non-operable embodiments showed the generic claims lacked written description. This allegation is incorrect for several reasons. First, the claims are plainly *not* drawn to *all* proteins having at least about 90% similarity or at least about 90% identity to SEQ ID NO:11 or being encoded by a coding region having at least about 90% identity to SEQ ID NO:12. Rather, the claims are plainly drawn to *L-galactose dehydrogenases, wherein the LGDHs* have the recited levels of similarity or identity to SEQ ID NO:11 or 12. The skilled artisan would have a reasonable expectation that an LGDH, i.e., a protein that catalyzes the conversion of L-galactono-1,4-lactone + 2 ferricytochrome c to L-ascorbic acid + 2 ferrocytochrome c, regardless of its amino acid sequence, would be operable in the claimed methods.

In addition, the Court in *Capon v. Eshhar* addressed what is needed to support generic claims and held "It is not necessary that every permutation within a generally operable invention

be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic invention” (at 1085). Applicants discuss the generation of recombinant yeast at p. 11, line 26 to p. 17, line 2, and provide specific examples of coding region amplification, transformation into yeast, ascorbic acid production, and assay of same, at p. 23, line 30 to p. 31, line 5. Applicants cite 26 references discussing various aspects of the art and also cite Sambrook *et al.*, *Molecular Genetics: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, which is one of the best-known references for laboratory techniques, including techniques which can be used to prepare proteins having at least about 90% similarity or at least about 90% identity to SEQ ID NO:11 or being encoded by a coding region having at least about 90% identity to SEQ ID NO:12. On reading the teachings of the specification in light of the state of the art, the skilled artisan would consider the claims to have support according to the holdings of *Capon v. Eshhar*.

Finally, Applicant notes that the Examiner alleged that the recitations of claims 12-14 “merely provide an invitation to conduct experiments to determine which sequences within the claimed genus would meet the functional criteria recited in the claims.” The Examiner’s language here appears to be more appropriate to discussion of enablement than of written description. As stated in *Capon v. Eshhar* at 1086, “The Board’s position that the patents at issue were merely an ‘invitation to experiment...’ concerns enablement more than written description.” At no point in prosecution of this application has the Examiner rejected any claim for lack of enablement. In the parent application, US Ser. No. 09/630,983, the Examiner rejected claims that recited proteins having at least threshold levels of similarity or identity to particular enumerated sequences on the grounds of not being enabled, but those rejections for lack of enablement were withdrawn.

For any or all of the foregoing reasons, Applicants request the rejection of claims 12-14 under 35 U.S.C. §112, first paragraph, as lacking sufficient written description, be withdrawn.

VIII. CLAIMS APPENDIX

The claims that are the subject of the present appeal – claims 12-14 – are set forth in the attached Claims Appendix, p. 10.

IX. EVIDENCE APPENDIX

There is no Evidence Appendix for this appeal.

X. RELATING PROCEEDINGS APPENDIX

There is no Related Proceedings Appendix for this appeal.

XI. CONCLUSION

Applicants submit all pending claims 12-14 are in condition for allowance.

Respectfully submitted,

WILLIAMS, MORGAN & AMERSON, P.C.
CUSTOMER NO. 23720

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/Raymund F. Eich/
Raymund F. Eich, Ph.D.
Reg. No. 42,508
10333 Richmond, Suite 1100
Houston, Texas 77042
(713) 934-4065
(713) 934-7011 (fax)

AGENT FOR APPLICANTS

CLAIMS APPENDIX

Claim 12. A method of generating ascorbic acid, comprising:

- a) obtaining a recombinant yeast capable of converting an ascorbic acid precursor into ascorbic acid, wherein the yeast is functionally transformed with a coding region encoding L-galactose dehydrogenase (LGDH) enzyme having at least about 90% similarity with SEQ ID NO:11,
- b) culturing the recombinant yeast in a medium comprising an ascorbic acid precursor, thereby forming ascorbic acid, and
- c) isolating the ascorbic acid.

Claim 13. A method of generating ascorbic acid, comprising:

- a) obtaining a recombinant yeast capable of converting an ascorbic acid precursor into ascorbic acid, wherein the yeast is functionally transformed with a coding region encoding L-galactose dehydrogenase (LGDH) enzyme having at least about 90% identity with SEQ ID NO:11,
- b) culturing the recombinant yeast in a medium comprising an ascorbic acid precursor, thereby forming ascorbic acid, and
- c) isolating the ascorbic acid.

Claim 14. A method of generating ascorbic acid, comprising:

- a) obtaining a recombinant yeast capable of converting an ascorbic acid precursor into ascorbic acid, wherein the yeast is functionally transformed with a coding region encoding L-galactose dehydrogenase (LGDH) enzyme and the coding region encoding the LGDH enzyme has at least about 90% identity with SEQ ID NO:12,
- b) culturing the recombinant yeast in a medium comprising an ascorbic acid precursor, thereby forming ascorbic acid, and
- c) isolating the ascorbic acid.

EVIDENCE APPENDIX

None.

RELATED PROCEEDINGS APPENDIX

None.